UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JOACHIM HERZ and PETRA MAY

Appeal No. 2006-2556
Application No. 09/977,155

ON BRIEF

Before SCHEINER, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to methods for detecting proteolysis of a low density lipoprotein (LDL) receptor. The examiner has rejected the claims as anticipated. We have jurisdiction under 35 U.S.C. § 134. We reverse.

Background

"[R]ecent genetic experiments have revealed critical functions for LDL receptor family members in the transmission of extracellular signals and the activation of intracellular tyrosine kinases. This process regulates neuronal migration and is crucial for brain development." Specification, page 1.

The specification discloses "that members of the LDL receptor gene family undergo endoproteolytic processing events that result in the release of their cytoplasmic tails into the cytoplasm." Id. Thus, "[t]he invention provides methods and compositions for modeling and detecting LDL receptor transmembrane signaling by detecting proteolysis of an LDL receptor transmembrane domain." Id. at page 2.

The specification discloses that proteolytic cleavage of the LDL receptor transmembrane domain can be assayed by detecting the release of the C-terminal tail from the cell membrane. Id. For example, the C-terminal tail can be fused to a detectable marker such as a transcription factor domain which, when released from the membrane by proteolytic cleavage, will trigger expression of a responsive reporter. Id.

Discussion

1. Claim construction

Claims 1-20 are pending.

The examiner has objected to claim 10 as being dependent upon a rejected base claim, but has indicated that it would be allowable if rewritten in independent form including all of the limitations of the base claim. See Examiner's Answer, page 6.

Claims 1-9 and 11-20 are on appeal.

Appellants have not argued the claims separately. Therefore, the claims subject to each rejection stand or fall together. 37 CFR § 41.37(c)(1)(vii). Claims 1 and 15 are representative and read as follows:

> 1. A method for detecting proteolysis of an LDL (Low Density Lipoprotein) receptor transmembrane domain, comprising the steps of:
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> a) providing a sample comprising a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a

C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane;

b) incubating the sample under conditions wherein the protease cleaves the domain and thereby releases the tail from the membrane; and

c) detecting a resultant released tail, which indicates proteolysis of the LDL receptor transmembrane domain.

15. A method according to claim 1, wherein the LDL receptor is LRP1b and the protease is native to the membrane.

Thus, claim 1 is directed to a method for assaying the proteolysis of an LDL receptor transmembrane domain by detecting the release of the C-terminal tail from the remainder of the membrane-bound protein.

The method involves incubating a cell membrane that contains a protease and an LDL receptor transmembrane domain fused to a C-terminal tail, under conditions that allow the protease to cleave the transmembrane domain and release the C-terminal tail from the membrane. Detection of the released tail indicates that the proteolytic cleavage has occurred.

Claim 15 limits the process of claim 1 to one in which a specific LDL receptor (LRP1b) is cleaved and the protease is one that is native to the membrane.

2. Anticipation by Willnow

Claims 1-9 and 11-14 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Willnow.[1]

The examiner points out that Willnow teaches "methods involving LRP-mini[]receptors," which are truncated versions of the low density lipoprotein receptor-

[1] Willnow et al., "Molecular Dissection of Ligand Binding Sites on the Low Density Lipoprotein Receptor-related Protein," The Journal of Biological Chemistry, Vol. 269, No. 22, pp. 15827-15832 (1994).

related protein (LRP). Answer, page 3 (citing Willnow, abstract). Willnow uses the truncated forms of the LRP to study the ligand binding properties of the receptor. See Willnow, abstract, and paragraph spanning pages 15287-15288.

The LRP-minireceptors prepared by Willnow are composed of either region II or region IV of the extracellular domain of the LRP, fused to the transmembrane portion of the protein and the C-terminal cytoplasmic tail. Willnow, page 15828, right column, first paragraph, and Figure 1. Thus, Willnow's modifications of the LRP are all in the portions of the protein outside the cell membrane, between the transmembrane domain and the N-terminus. See Willnow, Figure 1.

The examiner points out that region IV of the LRP contains a proteolytic site which allows the minireceptor having region IV to be cleaved into an 80 kDa amino-terminal fragment and an 85 kDa carboxyl-terminal fragment. Answer, page 4. In detecting expression of the LRP minireceptors in cells transfected with the gene for the region IV minireceptor, Western blotting indicated the presence of the protease-cleaved 80 kDa amino-terminal fragment and 85 kDa carboxyl-terminal fragment, as well as the unprocessed precursor. Id. (citing Willnow, paragraph spanning pages 15828 and 15829, and Figure 2).

Thus, the examiner urges that claim 1 encompasses the proteolytic processing of the region IV minireceptor described by Willnow.

Appellants argue that, contrary to claim 1's requirement that the proteolytic cleavage release the protein's carboxyl terminus from the membrane, "Willnow describes an LRP which is cleaved at an N-terminal, extracellular site, and the protease does not and cannot release from the membrane any C-terminal tail." Appeal Brief,

page 3. Appellants urge that the 85 kDa carboxyl-terminal fragment visualized by Western blotting "is released from the membrane not by the protease, but rather by subsequent biochemical extraction." Id. at page 4

Appellants point out that "[i]n Willnow, protease cleavage at the N-terminal, extracellular region IV processing site yields a membrane-bound fragment. The membrane-bound C-terminal cleavage produc[t] is then biochemically extracted from the membrane. In contrast, our claims require that cleavage by the protease release the tail from the membrane, which does not and cannot occur in Willnow's work." Id. (emphasis in original).

"To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997).

In our view, the examiner has not shown that Willnow discloses a protease that cleaves the transmembrane domain of an LDL receptor, resulting in release of the C-terminal tail from the cell membrane. We therefore agree with Appellants that the examiner has not demonstrated that Willnow anticipates claim 1.

We agree with Appellants that claim 1 requires the protease to "release[] the tail from the membrane." The only tail recited in claim 1 is the C-terminal tail. Thus, claim 1 explicitly requires the cleavage of the protein to release the C-terminal tail from the cell membrane.

The protease disclosed in Willnow cleaves the extracellular portion of the LRP. Willnow, Figure 1 (cleavage site in region IV indicated by arrows). By cleaving the extracellular portion of the protein, Willnow's protease leaves the entire C-terminal

portion of the protein intact. Thus, the cytoplasmic C-terminal tail remains attached to the protein's transmembrane domain, and therefore also remains attached to the cell membrane. By contrast, claim 1 requires that the protease "release[] the tail from the membrane."

The examiner argues that Appellants improperly seek to import the limitation requiring cytoplasmic release of the C-terminal tail from the specification into the claims. Answer, page 7. We do not agree. As pointed out supra, claim 1 requires the protease to "release[] the tail from the membrane," and the only tail recited in claim 1 is the C-terminal tail. Thus, in our view, one need only look to the limitations of claim 1 to conclude that Willnow does not anticipate the claim.

The examiner also argues that, because claim 1 uses open "comprising" language to describe the process, claim 1 encompasses additional steps not recited in the claim, including Willnow's biochemical extraction steps urged by Appellants as releasing the C-terminal tail from the membrane. Answer, page 8.

We agree with the examiner that the language of claim 1 encompasses additional process steps not recited in the claim. However, in our view, Willnow does not anticipate claim 1 because, as discussed supra, the reference does not disclose a protease that releases the C-terminal tail from the cell membrane. Thus, the fact that claim 1 encompasses additional steps does not negate the fact that Willnow fails to disclose a limitation explicitly recited in the claim.

To summarize, we agree with Appellants that Willnow does not describe a protease that cleaves the transmembrane domain of an LDL receptor, resulting in

release of the C-terminal tail from the membrane. We therefore reverse the anticipation rejection of claims 1-9 and 11-14.

3. Obviousness

Claims 15-20 stand rejected under 35 U.S.C. § 103(a) as being obvious over Willnow in view of Herz.[2]

The examiner acknowledges that Willnow differs from the claims "in not teaching all the possible LDL receptor[s] (namely LRP, LRP1b, megalin, LDLR, VLDLR, ApoER2, MEGF7, LRP5, LRP6, and LR11)." Answer, page 5.

However, the examiner points out that Herz discloses that "[t]he core members of the LDL receptor gene family include the LDL receptor, LRP, megalin, VLDL, ApoER2, LrP1b, and MEGF7," and that these core members of the LDL receptor gene family are closely related structurally. Id. (citing Herz, at page 571, first column, second paragraph). The examiner urges that one skilled in the art would therefore have considered it obvious "to use various known LDL receptor equivalents having similar structures and found native to the membrane as taught by Herz in the method of Willnow et al. because Herz taught that the LDL receptor gene family consists of seven structurally related cell surface receptors." Id.

Appellants argue that "nowhere does Herz disclose or suggest producing and detecting a protease liberated C-terminal tail of any LD[L] receptor as required by our claims." Appeal Brief, page 5.

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[2] Herz, "The LDL Receptor Gene Family: (Un)Expected Signal Transducers in the Brain," Neuron, Vol. 29, pp. 571-581 (March, 2001).

"In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.'" In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citations omitted, bracketed material in original).

We agree with Appellants that the examiner has failed to establish the prima facie obviousness of claims 15-20.

Each of claims 15-20 depends from claim 1. As discussed supra, claim 1 requires the use of a protease that cleaves the transmembrane domain of an LDL receptor, resulting in release of the C-terminal tail from the membrane. As also discussed supra, Willnow does not disclose a process in which a protease cleaves the C-terminal tail of an LDL receptor from a cell membrane.

The examiner has not pointed to, and we do not see, any teaching in Herz that remedies this deficiency in Willnow's disclosure.

We agree with the examiner that Herz discloses that the proteins recited in claims 15-20 are members of the LDL receptor gene family. However, we see nothing in Herz suggesting that it would have been obvious to assay for the activity of a protease that cleaves the C-terminal tail of a receptor from the cell membrane, as required in claims 15-20. We therefore reverse the obviousness rejection of claims 15-20.

Summary

Because Willnow does not disclose all of the limitations recited in claims 1-9 and 11-14, we reverse the anticipation rejection of those claims. Because Willnow and Herz do not suggest practicing the invention recited in claims 15-20, we reverse the obviousness rejection of those claims.

REVERSED

Toni R. Scheiner)
Administrative Patent Judge)
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